THE BRITISH JOURNAL
OF
DERMATOLOGY
JUNE 1960

LICHEN MYXOEDEMATOSUS.

A. J. M. JOHNSTON.

THE past decade has seen a remarkable revival of interest in diseases affecting fibrous connective tissue. The concept of collagen disease, arising primarily from the fundamental studies of Klinge (1933) and Klemperer *et al.* (1941) has come to denote a group of conditions characterized by rather specific degenerative and proliferative changes involving three elements, fibres, ground substance and cells. Emphasis however has been placed on the fibres and ground substance, while the living element, the cell, has been relatively neglected.

As fibrous connective tissue is distributed throughout the organs and systems of the body, it is not surprising that the signs and symptoms of the collagen diseases are protean in their manifestations. The skin, nevertheless, remains the most accessible source of connective tissue for histological examination and with new histochemical techniques its study may contribute to the understanding not only of cutaneous collagen diseases but of disorders of connective tissue in other organs. It is surprising that many diseases of connective tissue appear on the one hand as sinister systemic disorders and on the other as apparently innocuous cutaneous conditions. Thus the group comprises not only diseases such as lupus erythematosus and scleroderma, but also unusual metabolic disorders such as calcinosis, amyloidosis and mucinosis. These last three, which have an extracellular deposit of abnormal material in common, are sometimes classed as degenerations, e.g. mucoid degeneration. The term degeneration would be more applicable however to the type of alteration of collagen fibres seen for example in senile elastosis (Percival *et al.*, 1949).

In classifying the mucinoses, Palitz and Brunner (1950) separated them into two broad divisions, viz., catabolic and metabolic. In the former group they placed the myxomatous tumours, regarding them as degenerations, while in the latter group they included the myxoedemas which they did consider to be

degenerative. Their subdivision of the metabolic mucinoses into four types may be paraphrased as follows.

(i) Generalized myxoedema with hypothyroidism.
(ii) Localized myxoedema with hypothroidism (rare).
(iii) Pretibial myxoedema with hyperthyroidism.
(iv) Lichen myxoedematosus with normal thyroid function.

In all important respects this classification is similar to that presented by Montgomery and Underwood (1953) in their review of lichen myxoedematosus. These authors described in detail the clinical and pathological patterns of the latter which they grouped in the following manner.

(i) Discrete papular forms.
(ii) Localized to generalized lichenoid plaques.
(iii) Urticarial nodules and plaques becoming lichenoid.
(iv) Generalized lichenoid papular eruption (scleromyxoedema).

It is almost certain that these four types are not distinct entities but simply variants of lichen myxoedematosus, for in the case I am about to describe, features of all four were blended. For this reason, it is thought that a detailed report of the case might be of general interest and although no claims are made for originality, it is hoped that the histopathological bias of the presentation may provoke controversy.

Case Report.

A married woman, aged 48, was first seen in May 1957. She complained that small tumours had appeared about three years previously in the skin on the back of the left wrist and had gradually spread to her arms, knees and face. She felt perfectly well and the lesions gave rise to no symptoms. She had given birth to nine children and had a total hysterectomy at the age of forty-four because of severe menorrhagia. The uterus was found to be normal and although the ovaries were left *in situ*, she experienced menopausal symptoms shortly after the operation and began to gain weight. She also began to suffer from painful but transient swelling of the hands which was thought to be due to rheumatoid arthritis. Her mother died of diabetes, but there was no other evidence of familial disease.

On examination.—Clusters of discrete, pale yellow, waxy nodules, varying in size from a pinhead to a pea, were seen on the back of the wrists and along the ulnar border of the forearms (Fig. 1). The nodules were smooth, rounded and firm to the touch and were not tender when firmly pressed. Some of the lesions had coalesced to form rubbery, pink plaques in which the individual nodules could still be felt though not seen. Lichenoid plaques were also present over the knees (Fig. 2) and elbows, while the skin on the outer aspect of the upper arms was covered with a fine papular eruption which gave it a gooseflesh appearance and made it feel firm, thick and leathery. Small papules were scattered over the face and ears and formed a beaded chain around the vermilion border of the lips, nares and philtrum. Although the backs of the fingers were also covered with plaques, the joint creases were spared and no limitation of movement was noted. The lesions tended to be distributed symmetrically on exposed and extensor surfaces. When the generalized papular rash on the arms was examined

under the hand-lens, the individual lesions could be seen to occur in parallel lines along the ridges of the skin. Follicular openings could be seen between but not on the papules, while fine telangiectatic vessels branched between the lesions, giving the area a rosy erythema when the patient became warm.

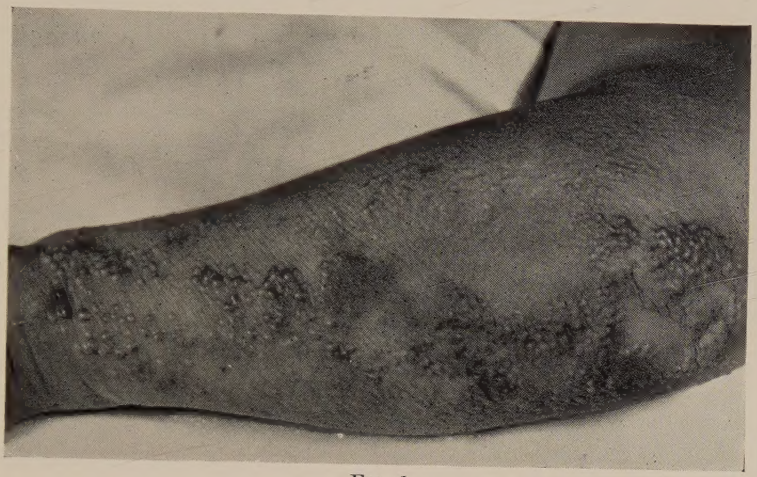

FIG. 1.

FIG. 2.

The skin and its appendages appeared otherwise normal, while a physical examination revealed no systemic abnormalities other than obesity and some tender swelling around the second and third metacarpophalangeal joints of both hands, indicative of rheumatoid arthritis.

The patient was admitted to hospital for investigation. The differential diagnosis included the lipoidoses, reticuloses, amyloidosis cutis, lichen myxoedematosus, and lichen ruber moniliformis. Histological examination confirmed the diagnosis of lichen myxoedematosus.

Investigations.—No abnormalities were detected in skiagrams of the chest and pituitary fossa, or in electrocardiographic tracings. Red and white blood cell counts, routine analysis of the urine and serum electrolyte and blood urea nitrogen determinations were all normal. The electrophoretic pattern of the serum protein was normal on four occasions, but both the serum gamma globulin fraction and the blood sedimentation rate were raised on one occasion when her rheumatoid arthritis was active. The twenty-four hour urinary excretion of ascorbic acid, nor-adrenaline, pregnandiol, 17-ketosteroids and acid stable formaldehydic hormone was normal, as were liver function tests including the serum thymol turbidity reaction, the serum carotene and bilirubin levels, acid and alkaline phosphatase activity and the glucose tolerance curve.

No evidence of any systemic disorder was discovered until the blood lipids were studied and the following results were obtained.

Serum total cholesterol, 348 mg./100 ml.	Plasma total cholesterol, 300 mg./100 ml.
,, free cholesterol, 103 mg./100 ml.	Beta lipoprotein cholesterol, 260 mg./100 ml.
,, fatty acids, 434 mg./100 ml.	Alpha : beta lipoprotein ratio, 13·87
,, lipid phosphorus, 5 mg./100 ml.	Cholesterol/phospholipid ratio, 1·05

Repeated tests confirmed these findings, but their significance could not be ascertained. It was thought that they reflected the patient's obesity rather than thyroid dysfunction or the abnormal state of the skin. The B.M.R. was −3% of normal and the results of the radioactive iodine uptake and excretion estimations confirmed the clinical impression that the patient was euthyroid. The skin lesions did not take up the isotope.

Histopathology.—Several nodules and papules were excised from the left wrist for histological study. The main pathological change was seen in the subpapillary portion of the dermis (Fig. 3). In the overlying epidermis the outlines of the rete pegs were obliterated, presumably as a result of pressure, but in all other respects the epidermis was normal. The silver stain failed to reveal excess melanin. In the upper dermis there were clearly delimited areas in which the collagen fibres were frayed, split and widely separated. Although many of the fibres were shredded into their constituent fibrils, they stained normally with a variety of collagen stains, while fibrin stains showed no evidence of fibrinoid degeneration. Both reticulin and elastic fibres could be demonstrated with selective stains and though they were sparsely distributed within the lesions, their apparent diminution was proportionally no greater than that of the collagen fibres. Many elliptical connective tissue cells were scattered throughout the lesions. The majority of the cells appeared to be fibroblasts, a few were presumed to be histiocytes, while a proportion of the cells were stellate and resembled myxoma or primitive mesenchymal cells. Occasionally a cell was seen in mitotic division, but there were no abnormal mitotic figures. Although a variety of fixatives and metachromatic stains was used, cytoplasmic granules could not be demonstrated.

The spaces between the collagen fibres and cells appeared to be empty in routinely fixed and stained specimens and neither lipids nor amyloid could be demonstrated in frozen sections. When alcohol-fixed specimens were stained with toluidine blue or polychrome methylene blue, however, a network of fine strands of metachromatically stained material could be seen between the fibres (Fig. 4). This substance was also demonstrated by the dialyzed iron method of Hale (1946) and the alcian blue method of Mowry (1956), but not by the P.A.S. reaction of McManus (1946) or various modifications of mucicarmine staining.

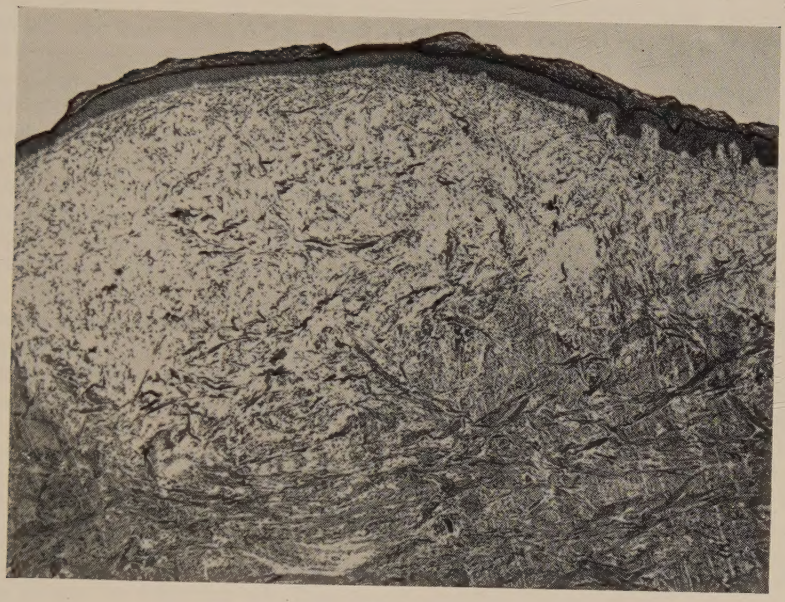

FIG. 3.

FIG. 4.

Alcian blue proved to be a most satisfactory stain. It dyed the network of abnormal material bright blue, while a variety of background stains such as safranine or the Feulgen procedure could be used to colour the fibres and cells for contrast. In alcohol-fixed specimens, it was noted that the fine threads of alcian blue positive material frequently widened into amorphous, homogeneous masses, thus confirming the impression that the fibrillar appearance of the substance was an artefact. As Cawley and his associates (1957) observed, the ends of the collagen fibres sometimes seemed to merge imperceptibly with the alcian blue positive material. Although the fibroblasts did not take up the stain, the coloration was frequently most intense around them. It has been claimed that alcian blue, when properly adjusted to the right dilution and pH, is a specific stain for the acid mucopolysaccharides, It was decided to test this specificity by incubating sections in bovine testicular hyaluronidase which is known to depolymerize and hydrolyse hyaluronic and chondroitin sulphuric acids. After four hours' incubation, most of the alcian blue positive material was removed and after twelve hours the removal was complete. No loss of alcian blue positive material was observed in the control sections incubated in saline. From this it was deduced that alcian blue was specifically staining a material which contained acid mucopolysaccharides.

When specimens were serially sectioned, dilated but intact capillaries were almost invariably found within the lesions, extending for a variable distance in the surrounding skin mostly in the subpapillary plexus. In many instances, these neighbouring dilated capillaries were surrounded by a cluster of connective tissue cells, some of which showed mitotic figures. Sometimes this perithelial cellular proliferation was accompanied by separation of collagen fibres and the presence of mucin staining material. These changes were thought to indicate that new lesions were commencing in these sites. Although smooth muscle fibres were occasionally found in the lesions, no pilo-sebaceous follicles or sweat glands were seen. The appearance of these structures in the surrounding skin was normal.

When the thick, leathery skin of the arms was examined in serial sections, lesions were found which were similar in histological type to the nodular eruption on the wrists but differed in size and distribution. In this area, widespread vascular dilatation was seen in the papillary and also in the lower layers of the dermis. At short almost regular intervals, the characteristic pathological alterations were seen around subpapillary vessels. The overlying rete pegs were not obliterated as in the case of the nodular lesions, but were slightly flattened. In addition, small lesions were seen periodically around deeper vessels, particularly those vessels associated with sweat glands and ducts. These appendages were however in no way altered.

After an interval of two years, the skin of the left forearm was again examined histologically. By this time the eruption had almost completely regressed and the only visible lesions in this area were small inconspicuous flat papules. Nothing abnormal could be seen in the sections. The rete pegs extended downward in the normal manner, the collagen fibres had regained their normal arrangement, the usual number of fibroblasts were present and no mucin could be detected.

Chemical analysis.—The staining characteristics of the mucinous infiltrate indicated that this material contained a mucopolysaccharide, while the effect of hyaluronidase, both *in vivo* and *in vitro*, suggested that the mucopolysaccharide might be partly hyaluronic acid. The staining reactions were, however, inconstant and it was thought that more conclusive information could be obtained by chemical analysis of the diseased skin. For this purpose an elliptical piece of skin about an inch and a half long was excised from a thick plaque on the patient's left wrist.

The primary object was to separate the mucopolysaccharides, namely hyaluronic acid and chondroitin sulphuric acid, from the skin and by means of the Elson-Morgan colour reaction to determine the amounts of mucopolysaccharides present. This was unsuccessful because of the difficulty in extracting the mucopolysaccharides quanti-

tatively. It was however possible, without preliminary extraction, to determine the mucopolysaccharide as hexosamine. The skin was defatted and dissolved in alkali. The mucopolysaccharides were precipitated from the solution with alcohol and converted into hexosamine by acid hydrolysis. The residue was then treated with a solution of acetylacetone to produce a complex which gave a characteristic pink coloration with Ehrlich's reagent. By relating the optical density of the solution to standards, the amount of hexosamine present could be measured.

Johnston, Ogston and Stanier (1951), whose modification of the Elson-Morgan technique was adopted for this investigation, have claimed accuracy to within 3% for their determinations of hyaluronic acid even in the presence of large amounts of protein. However, the results must be viewed with some reserve as certain pyrrole derivatives and the tryptophane nucleus colour with Ehrlich's reagent. The advantage of the method is that it permits the determination of hexosamine in as little as 0·25 g. of skin. The main disadvantage lies in the loss of material incurred during the process of extraction. In each determination, 0·25 g. of skin was used. It was fresh and not previously defatted or dried before weighing. The results are presented in Table I.

TABLE I.—*The Hexosamine Content of the Skin.*

Source of skin.	Number of results.	Mean hexosamine content (mg./0·25 g.).	Standard deviation.	As percentage.	Range (mg./0·25 g.)
Normal skin of man aged 55–60 years	5	71·6	±2·8	3·9	69–74·5
Skin of woman with lichen myxoedematosus	4	401·25	±37·5	0·2	354–438

Thus there appeared to be a large increase in the mucopolysaccharide content of the skin, expressed as hexosamine. It could not be determined whether the increase was in hyaluronic acid or the chondroitin sulphuric acid fraction.

In 1947, Watson and Pearce (1947) determined the mucopolysaccharide content of plaques from the skin of two patients with circumscribed pretibial myxoedema and found a large increase of mucopolysaccharide substances believed to be hyaluronic acid and chondroitin sulphuric acid. Their results for the hexosamine content of the pieces of skin used as controls were compared with those in the present case in order to obtain some idea of the range over which the hexosamine content varied (Table II). Taking the mean values, i.e., 54 and 42 mg.%, and calculating the weights of hexosamine present from these values, the weights of hexosamine from the two sets of determinations were found to be in the same range, viz., 0·23 mg./g. in their determinations, 0·28 mg./g. in mine. It was inferred that the method used in my case

TABLE II.—*The Hexosamine Content of Normal Skin.*

Source.	Hyaluronic acid (mg./100 g. skin).	Chondroitin sulphuric acid (mg./100 g. skin).	Total mucopolysaccharide (mg./100 g. skin).
Normal skin from 9 amputated legs	26 ± 9	28 ± 6	54 ± 15
	Hexosamine hyaluronic acid	% Hexosamine in chondroitin sulphuric acid	% Hexosamine in total mucopolysaccharides
	22 ± 8	20 ± 5	42 ± 13

(Adapted from Watson and Pearce.)

was comparable in accuracy with the method of Watson and Pearce. Unfortunately, the information obtained was much more limited.

Treatment and progress.—Various destructive measures including freezing with carbon dioxide snow and liquid nitrogen, painting with phenol, probing with trichloracetic acid and electrical fulguration were tried to remove the most disfiguring lesions from the patient's face. Some scarring resulted from all the methods, but acceptable cosmetic results were obtained with the use of trichloracetic acid and electrical fulguration with a fine needle. Although clear zones were noted around the treated sites and biopsy scars, new papules developed in the two-inch scar on the wrist from which tissue had been removed for chemical analysis. As the scar shrank down, however, the papules disappeared. Various solutions were injected into the thick plaques on the knees. Sterile water and normal saline produced only transient oedema, while solutions of hydrocortisone acetate and hydrocortisone acetate mixed with hyaluronidase were equally ineffectual. The injection of 1500 i.u. of testicular hyaluronidase in water, however, was followed in ten minutes by inflammation and in thirty minutes by softening and flattening of the plaques. Although the effects of the injection were augmented by firm strapping with an adhesive bandage, the results were transitory and in thirty-six hours the plaques had regained their former size and shape.

Despite the absence of any obvious endocrine disorder, an empirical trial of oral hormones was made. Oestrogens produced nausea but no amelioration of the skin condition and no improvement was noted after the daily administration of 30 mg. of prednisolone for a month. The patient was then put on a reducing diet and given 1½ gr. of thyroid daily for six weeks. At the end of this time, slight improvement was thought to have occurred and the dose of thyroid was slowly raised to 3 gr. a day. As no ill effects were observed, it was decided to maintain the patient on this dosage for a year in view of her high serum cholesterol content. During the next six months it became increasingly apparent that the eruption was slowly improving. This improvement however was intermittent and localized, rather than progressive and generalized. Many plaques and isolated nodules flattened out and came to resemble papules of lichen planus which disappeared without a trace after some months. It could be clearly seen from photographs however that some lesions had remained completely unaltered.

The patient was re-examined in December 1958. At that time she appeared to be in good health though considerably thinner. The serum cholesterol and lipoprotein values were within the normal range and the electrophoretic serum protein pattern was normal. The skin lesions were now reduced to a few inconspicuous papules and nodules on the wrists and face and flat lichenoid patches on the elbows. The skin on the outer aspect of the arms had regained much of its normal appearance and texture, but the telangiectasia had persisted. At this point, treatment with thyroid was discontinued for four months. She was seen again in May 1959. Although she had gained a little weight, she was still robust and active. Her skin lesions had continued to fade although a few of the nodules on the wrists were as large as ever. The lichenoid patches on the elbows had almost completely flattened and a biopsy specimen from this area showed no pathological changes. The serum cholesterol, however, had risen to its previous level. In these circumstances it was decided to renew the thyroid medication.

Discussion.

The essential pathological change in lichen myxoedematosus is the presence of mucoid material between the connective tissue fibres of the dermis, accompanied by a proliferation of connective tissue cells. The accumulation of the

mucoid material could be attributed to the activity of these cells, but on the other hand they may have appeared as a result of the mucoid infiltration, in an attempt perhaps to lay down fresh collagen. If the latter supposition is true, the effort to form new collagen fibres was remarkably unsuccessful in the present case, for, as noted before, individual lesions remained apparently unaltered for two years, indicating that the mucinous material was either not reabsorbed or was constantly replenished during that time. It is generally held that fibroblasts are responsible for the formation of collagen fibres and contribute at least some material to the ground substance. Although there is no direct evidence that the mucinous material of myxoedematous states is identical with ground substance, the histochemical and biological reactions suggest at least close similarities. It is probable that this point could be settled if the newer techniques of tissue analysis by paper chromatography were applied to the problem (Bollet, 1958).

Much attention has been paid to the morphology of the connective tissue cells in myxoedematous skin. Asboe-Hansen (1958) has stressed the prevalence of Erlich's mast cells. Although no increase in the number of mast cells was seen in the sections from this patient, the histochemical technique may have been at fault, and the point cannot be debated. Other authors, e.g. O'Leary (1930) have emphasized the stellate outline of many of the cells and stellate cells are found in all myxoedematous tissues. They are common for example in ganglia, in myxomatous tumours and in Wharton's jelly as well as in the clinical myxoedemas. It might be inferred from this that the distinction between the catabolic and metabolic mucinoses may not be entirely valid.

A feature common to many myxoedematous tissues is the low level of oxidative activity. This would apply to foetal tissue, hypothyroid myxoedema and probably to degenerating tumours. In this respect, it has been claimed that hypothyroid myxoedema represents a reversion of fibroblast activity to the foetal level (Byrom, 1933). It is difficult, however, to see how this concept applies to lichen myxoedematosus.

Although the presence of stellate cells may aid in the diagnosis of myxoedema, it cannot be accepted that the shape of the cells is in any way responsible for their activity. It was shown many years ago (Harrison, 1911) that fibroblasts, when grown on a fibrous substrate in tissue cultures, adopt an elliptical shape in alignment with the fibres, but when the fibres are disrupted the cells send out radiating processes. It is conceivable that the disruption of collagen fibres in lichen myxoedematosus may similarly be responsible for the shape of the connective tissue cells. The collagen fibres were split and separated, but it could not be shown that they had degenerated and indeed the apparent loss of fibres was thought to be relative rather than absolute. It should be noted moreover that in the smallest and presumably the youngest lesions, perivascular cellular proliferation was more obvious feature than separation of collagen fibres.

Ogilvie (1952) noted similar fibroblastic proliferation in developing mucoid cysts, but in these, degeneration of collagen fibres eventually takes place. It must be admitted however that many investigators believe that degeneration of fibres occurs in myxoedematous skin (Reuter, 1931). Cawley and his associates (1957) drew attention to the apparent merging of collagen fibres with the alcian blue positive material. This appearance might be the result of a staining artefact or represent a mucinous coating of the fibres.

Although collagen degeneration is a questionable feature of lichen myxoedematosus, cellular proliferation, even mitotic division, can be seen. It is therefore difficult to assign a purely passive role to these cells in the pathogenesis of the disease. Meyer (1950 and 1952) suggested that the fibroblasts secreted hyaluronic acid which formed a loose linkage with the proteins of the substrate. He implied that the polymerization of this polysaccharide-protein complex is under enzymatic control by hyaluronidase. It is almost certain that hyaluronic acid is not only an important component of normal ground substance, but that it is also present in increased amounts in myxoedematous tissue. Unfortunately, there is no conclusive evidence that hyalyronidase exists in either normal or diseased skin and in view of this the suggestion that lichen myxoedematosus results from a local disturbance of enzymes in the skin must be treated with reserve.

The reason for the multiplication of the cells is also unknown. Vascular dilatation, perivascular cellular proliferation and even an increase in ground substance are in no way unique in lichen myxoedematosus, these changes being seen for instance in healing wounds, evidently as a response to local chemical and physical stimuli consequent to injury. It is clear that similar changes can also be produced by general disorders, e.g. the myxoedema of hypothroidism. The search for a systemic cause of lichen myxoedematosus has not however yielded convincing results.

Kleining and Braun-Falco (1956) reported a case of lichen myxoedematosus of the scleromyxoedema type in which they detected abnormalities of serum protein-bound carbohydrates possibly resulting from liver damage. They appear to support the view of Gottron (1954) and Tappeiner (1955) that abnormal proteins seep through the dilated capillaries to form pathological complexes with the mucopolysaccharides secreted by the fibroblasts. Dalton and Seidell (1953) found no abnormal serum mucoproteins in their case but noted a rise in the gamma globulin fraction. No such changes were found in the case under discussion, but the lipoproteins were abnormal. The importance of these changes in the pathogenesis of the disease is diminished by their non-specific character.

Despite the close similarities between generalized myxoedema, pretibial myxoedema and lichen myxoedematosus, it has never been proved that there is an underlying endocrine disorder common to all. It has been suggested that

the first two conditions might result from an excess of thyroid stimulating hormone (1956) but no pituitary or thyroid imbalance can be detected in lichen myxoedematosus. Nevertheless, in the case reported, a remission was noted which coincided with the administration of large doses of thyroid over a long period of time. Although the improvement may have been spontaneous and quite unrelated to the administration of thyroid, there is some evidence that thyroxin may assist the maturation of connective tissue. For instance, the addition of thyroid extract to tissue cultures favours the growth of fibroblasts. It is just possible therefore that the thyroid medication exerted a favourable pharmacological effect on the skin in spite of the absence of demonstrable thyroid disease. A trial of prolonged and vigorous thyroid therapy may therefore be justified in severe or disfiguring cases of lichen myxoedematosus.

There seems little liklihood that the problem of the aetiology of lichen myxoedematosus can be solved by histological or even histochemical means. Useful information will undoubtedly be gained from improved methods of tissue extraction and analysis, but the study of living cells in tissue culture would seem the most fruitful approach.

The essence of this rare and obscure disease is a lack of balance between the three components of connective tissue, viz., the cells, fibres, and ground substance. The cause of the condition may be discovered when the fundamental relationship between these three elements in normal tissue is better understood. It is remarkable that the question of this relationship, originally raised by Kölliker, remains unanswered after almost a century of investigation.

Summary.

The classification of the myxoedemas and of the varieties of lichen myxoedematosus is briefly reviewed.

A case of lichen myxoedematosus occurring in a middle-aged woman is reported. The lesions varied from small papules to large nodules and lichenoid plaques and occurred mainly on the face and the extensor surfaces of the limbs. An unusual feature was a leathery thickening of the skin of the arms.

Thorough investigation revealed no systemic abnormalities other than a moderate elevation of the serum cholesterol, associated with changes in the alpha : beta lipoprotein ratio. No endocrine disorder was detected.

The histopathological changes were seen mainly in the upper dermis and consisted of delimited areas in which the collagen fibres were split, separated and surrounded by amorphous material which stained with dyes said to be specific for the acid mucopolysaccharides. These changes were associated with the proliferation of connective tissue cells which were thought to originate in the perithelium of dilated capillaries.

The amorphous material between the fibres was removed by hyaluronidase *in vitro* and injections of hyaluronidase into the skin lesions *in vivo* produced temporary softening.

A large increase in the hexosamine content of the dermis was revealed by chemical analysis of the diseased skin.

Many disfiguring lesions were removed by electrical fulguration and by probing with trichloracetic acid. Oestrogen and steroid therapy produced no improvement, but a remission was noted coincident with the prolonged administration of large doses of thyroid extract.

It was concluded that the pathological alterations in the ground substance and collagen fibres were mediated by the connective tissue cells, but how they produced these changes and what caused them to proliferate could not be discovered.

I am most grateful to Professor G. H. Percival for permission to investigate his patient and for his invaluable help in the preparation of this paper.

I would also like to express my gratitude to Dr. A. G. Macgregor and Dr. M. F. Oliver for their assistance in the clinical and biochemical investigations. I am indebted to Mr. T. E. Isles for the chemical analyses and to Mr. T. C. Dodds for the clinical photographs and photomicrographs. Very valuable technical assistance was given by Mr. J. Waugh, Mr. J. Atherton, and Miss S. L. M. Heath.

[The author, who died in 1959, completed this study whilst Registrar to the Dermatological Department of Edinburgh Royal Infirmary. Requests for reprints of this paper should be addressed to the Editor.]

References

Asboe-Hansen, G. (1958) *Acta derm.-venereol., Stockh.*, **30**, 338.
Bollet, A. J. (1958) *J. clin. Invest.*, **37**, 858.
Byrom, F. B. (1933) *Clin. Sci.*, **1**, 273.
Cawley, E. P., Lupton, C. H., Wheeler, C. E. and McManus, J. F. A. (1957) *Arch. Derm., Chicago*, **75**, 537.
Dalton, J. E. and Seidell, M. A. (1953) *Arch. Derm. Syph., Chicago*, **67**, 194.
Gottron, H. A. (1954) *Arch. Derm. Syph., Berlin*, **199**, 71.
Hale, C. W. (1946) *Nature, Lond.*, **157**, 202.
Harrison, R. G. (1911) *Science*, **34**, 279.
Johnston, J. F., Ogston, A. G. and Stanier, J. E. (1951) *Analyst.*, **76**, 88.
Keining, E. and Braun-Falco, O. (1956) *Acta derm.-venereol., Stockh.*, **36**, 37.
Klemperer, P., Pollack, A. D. and Baehr, G. (1941) *Arch. Path.*, **32**, 559.
Klinge, F. (1933) *Ergebn. allg. Path. path. Anat.*, **27**, 1.
McManus, J. F. A. (1946) *Nature, Lond.*, **158**, 202.
Meyer, K. (1950) In *Transactions of the First Connective Tissue Conference*, New York : Josiah Macy Jr. Foundation.
——— (1952) *Nature, Lond.*, **170**, 518.
Montgomery, H. and Underwood, L. J. (1953) *J. Invest. Derm.*, **20**, 213.
Mowry, R. W. (1956) *J. Histochem.*, **4**, 407.
Ogilvie, R. F. (1952) *Pathological Histology*, 5th ed. Edinburgh : Livingstone.
O'Leary, P. A. (1930) *Arch. Derm. Syph., Chicago*, **21**, 57.
Pallitz, L. and Brunner, M. J. (1950) *J. invest. Derm.*, **14**, 159.
Percival, G. H. (1956) In *IXme Congrès des Dermatologistes et Syphiligraphes de Langue Française*, Lausanne.
——— Hannay, P. W. and Duthie, D. A. (1949) *Brit. J. Derm.*, **61**, 269.
Reuter, M. J. (1939) *Arch. Derm. Syph., Chicago*, **24**, 55.
Tappeiner, J. (1955) *Arch. klin. exp. Derm.*, **201**, 160.
Verne, J. and Odiette, D. (1936) *C.R. Soc. Biol., Paris*, **122**, 988.
Watson, E. M. and Pearce, R. H. (1947) *Brit. J. Derm.*, **59**, 327.

IS *COLLAGÉNOME ÉRUPTIF* A SEPARATE ENTITY ?

M. J. WOERDEMAN, M.D.
Department of Dermatology and Venereology, Binnen-Gasthuis, Amsterdam.

In 1953 the name "*collagénome éruptif*" was given by Colomb to a dermatosis which in his opinion had not been described before. He used this term to indicate the histological changes which involved mainly the collagen bundles. The patient was a North African man aged 20 in whom persistent papular lesions on the trunk were noted after the disappearance of a transient syphilitic roseola following a course of penicillin. The small multiple papules were slightly raised and just palpable. They did not itch ; they were partly confluent and skin coloured. The histological changes consisted mainly of a degenerative and hypertrophic process involving the collagen bundles. Only certain of them in the corium were involved, appearing as brightly acidophilic islands in the affected areas. The collagen fibres were thickened, homogenized and arranged in a disorderly manner. The elastic fibres in the affected areas also showed degenerative changes, but to a lesser degree. Histologically, xanthomatosis and amyloidosis could be excluded. After two years the patient was re-examined and the clinical and histological pictures were unchanged (Duverne, Coudert and Colomb, 1955). It was neither clear whether the papules antedated the syphilis, nor whether they appeared together suddenly, or over a period of time. The latter seemed most probable.

Loewenthal (1957) pointed out that a close resemblance existed between cases of connective tissue naevus and Colomb's case of *collagénome éruptif*. He described four patients of which he regarded three as cases of connective tissue naevus and one a case of *collagénome éruptif*. This last patient, a negro aged 32, who developed his cutaneous lesions at the age of 22, closely resembled Colomb's patient clinically and histologically, but on the other hand also bore a close resemblance to the three cases of connective tissue naevus. Neither on clinical nor histological grounds could these two dermatoses be differentiated and in Loewenthal's opinion it seemed quite possible that both Colomb's case and his own could be regarded as examples of connective tissue naevi developing after adolescence.

As far as I know only one further case of *collagénome éruptif* has since been described (Gay Prieto, Rodriguez Perez and Alvarez Cascos, 1958). The patient was a man aged 44 who two years earlier had developed pinhead and millet seed sized, non-itchy, yellowish papules on the trunk and upper legs. Histologically, basophilic degeneration of the collagen bundles was seen under a

normal epidermis. Very few elastic fibres were present in the papules. With toluidine blue and thionin, a brightly red metachromatic substance was seen between the collagen fibres in the papules. There was a slight perivascular infiltrate and many mast cells. In the differential diagnosis only connective tissue naevus was mentioned.

Case Report.

In the University Clinic at Amsterdam a patient was seen in which we considered the diagnosis of *collagénome éruptif* on clinical grounds. The patient was a young man of partly Indonesian origin, aged 19. He had either congenital or acquired latent

Fig. 1.

syphilis. Three years previously, small, millet seed sized, yellowish, non-itchy papules appeared on the backs of his wrists (Fig. 1), his elbows and to a lesser degree his knees. The clinical picture, the patient's age and the co-existence of syphilis were features similar to those of Colomb's patient with *collagénome éruptif*. When a biopsy was performed (left elbow), a mucinous substance was released from a papule. Microscopically, the epidermis was normal but the corium appeared oedematous. The collagen fibres were thickened and partly fragmented. There was a slight perivascular, non-specific cellular infiltrate. In the deeper part of the corium, the elastic fibres were swollen and fragmented. With mucicarmine and toluidine blue, a metachromatic substance bordering clefts in the oedematous area was revealed. Probably most of the metachromatic substance had been lost but in other sections metachromasia in the middle and deep part of the corium was still visible. With the toluidine blue many mast cells were seen.

The histological picture was typical of lichen myxoedematosus. The clinical picture was that of the so-called discrete papular type of lichen myxoedematosus (Montgomery and Underwood, 1953).

Discussion.

The question therefore arises whether all cases of *collagénome éruptif* can be regarded as examples of the discrete papular type of lichen myxoedematosus. The clinical picture of the latter consists of small, yellowish or skin-coloured, non-itchy papules. To make the diagnosis of lichen myxoedematosus (a better name is mucinosis papulosa cutis, proposed by Dalton and Seidell, 1953) histological examination is necessary, especially with mucicarmine and toluidine blue to demonstrate the metachromatic mucin.

The histological picture in the case of Gay Prieto *et al.*, with the metachromatic areas in the toluidine blue preparations, is in my opinion typical of lichen myxoedematosus. Also, the clinical picture is similar to that of the discrete papular type of the latter. This rare dermatosis was not mentioned in their differential diagnosis. In a recent paper von Zezschwitz (1959) described a case of lichen myxoedematosus which he compared with the very similar case of Gay Prieto *et al.*, without stating definitely that the latter was one of lichen myxoedematosus. In the case record of Colomb's patient the appearance with toluidine blue stain was not described in detail and Loewenthal does not mention toluidine blue or mucicarmine preparations in his patients. Lichen myxoedematosus, therefore, cannot be excluded in these cases.

As has been pointed out by Loewenthal there also exists a close resemblance between *collagénome éruptif* and connective tissue naevus. It is not surprising that there is a close resemblance between *collagénome éruptif* and lichen myxoedematosus on the one hand and between *collagénome éruptif* and connective tissue naevus on the other hand ; various clinical forms both of lichen myxoedematosus and of connective tissue naevus exist which greatly resemble each other. Histologically there is also a close resemblance between these two rare dermatoses and a differential diagnosis is only possible if mucin stains are used. In connective tissue naevus, mucin stains give negative results (Prakken, 1952) in contrast to lichen myxoedematosus. Moreover, in cases of lichen myxoedematosus of long duration the differential diagnosis can often not be made as in these cases the mucin staining is mostly negative.

It becomes obvious that a differential diagnosis between *collagénome éruptif* and connective tissue naevus on the one hand or between *collagénome éruptif* and lichen myxoedematosus on the other is impossible. One of the three published cases of *collagénome éruptif* is probably a case of lichen myxoedematosus (discrete papular type) ; the other two cases are either cases of connective tissue naevus (as has been pointed out by Loewenthal) or cases of lichen myxoedematosus. Therefore it does not seem justified to consider *collagénome éruptif* a separate entity.

Summary.

The author describes a case of lichen myxoedematosus (discrete papular type) which at first was considered one of *collagénome éruptif*. Those published as the latter are regarded either as cases of connective tissue naevus or of lichen myxoedematosus. It is concluded that it is not justified to consider *collagénome éruptif* a separate entity.

References.

Colomb, D. (1953) *Les alterations du tissue conjonctif en dermatologie. Des collagénoses aux collagénomes.* Thesis, Lyons.
Dalton, J. E. and Seidell, M. A. (1953) *Arch. Derm. Syph., Chicago*, **67**, 194.
Duverne, J., Coudert, J. and Colomb, D. (1955) *Ann. Derm. Syph., Paris*, **82**, 160.
Gay Prieto, J., Rodriguez Pérez, P. and Alvarez Cascos, M. (1958) *Hautarzt*, **9**, 300.
Loewenthal, L. J. A. (1957) *Dermatologica, Basel*, **114**, 81.
Montgomery, H. and Underwood, L. J. (1953) *J. invest. Derm.*, **20**, 213.
Prakken, J. R. (1952) *Brit. J. Derm.*, **64**, 87.
Zezschwitz, K. A. v. (1959) *Arch. f. klin. u. exp. Dermat.*, **208**, 301.

THE IMMUNOPATHOLOGY OF LUPUS ERYTHEMATOSUS.*

P. A. MIESCHER, L. THOMAS, B. BENACERRAF, N. S. COOPER, E. FRANKLIN AND N. ROTHFIELD.

The Departments of Medicine and Pathology and the Rheumatic Diseases Study Group, New York University College of Medicine and Third Medical Division, Bellevue Hospital Center, New York, N.Y.

HAVING been involved for many years in research on immune reactions in systemic lupus erythematosus (SLE), we see one window open to the study of the immunopathology of discoid lupus erythematosus, since more and more data indicate that both pathological conditions reflect the same basic disease process, although with entirely different clinical consequences. Indeed, as early as 1872, the dermatologist Kaposi suggested that acute disseminated lupus erythematosus and chronic discoid lupus erythematosus represented the same nosological entity.

This relationship can be demonstrated in a number of ways. It is not uncommon to observe symptoms indicating a more general involvement in discoid lupus; furthermore, a certain number of patients with discoid LE gradually develop systemic LE (Ziff *et al.*, 1958). It is striking that among the last 54 Bellevue Hospital patients suffering from SLE a history of discoid LE was observed in 16·5%: 5 patients had discoid skin eruptions less than 1 year prior to the diagnosis of SLE; 3 showed such skin lesions for 4 to 10 years, and 1 patient for as long as 29 years prior to the first manifestations of systemic lupus erythematosus. This cannot be merely coincidental.

Other features, common to both conditions, which may be of significance in terms of the underlying pathogenesis are the peculiar sensitivity to sunlight and the beneficial action of antimalarial drugs.

On the basis of these data it seems highly probable that SLE belongs to the same nosological entity as discoid cutaneous LE. In order to get some insight into the pathogenic pathway of discoid lupus, it therefore seems logical to start with the known immune reactions in SLE.

It has been known for many years that patients suffering from SLE easily form antibodies against various antigens. Callender and Race (1946) described the appearance of no less than seven blood-group specific iso-antibodies in a patient with SLE who had received many transfusions. In past years many additional immune reactions have been described in this disease (Miescher and Vorlaender, 1957). Very striking is the fact that a great number of these reactions were directed against genetically determined,

* This work was supported in part by a grant from the John Polachek Foundation for Medical Research and was presented as a paper at a Symposium on Chronic Discoid Lupus Erythematosus held by the Section of Dermatology of the Royal Society of Medicine on 21 May 1959.

autologous antigenic substances. Thus serum factors directed against erythrocytes, thrombocytes, and clotting factors as well as against kidney, heart and liver-tissue and against thyroglobulin were detected. Another auto-antibody-like phenomenon is the Wassermann reaction which is not infrequently positive in SLE in the absence of syphilis. Finally the rheumatoid agglutinating factor, present in about one-fifth of these patients, seems to represent another immune phenomenon (Miescher and Straessle, 1959 ; Seligmann, 1959).

All of the above mentioned immune reactions are without clear-cut specificity for SLE. In the L.E. phenomenon and the underlying antinuclear factors, however, a group of immune reactions has been discovered which exhibit a high degree of specificity for the disease. Consequently an effort has been made to get some insight into the pathogenesis of SLE by the investigation of these antinuclear reactions.

Whereas the histological changes present in SLE can by no means be correlated with the first group of immune reactions, the well known haematoxylin bodies represent nuclear material similar to the inclusion body observed *in vitro* in the L.E. phenomenon. On the basis of this very important discovery by Klemperer and collaborators (1950), it is not surprising that the main approach to the study of the pathogenesis of SLE was focused in this direction.

In comparing the L.E. phenomenon to other known phagocytic phenomena, Capelli (1952), Marmont (1952) and one of us (Miescher *et al.*, 1953) proposed the hypothesis that the L.E. cell is the consequence of the action of an antinuclear antibody on leucocytes. In a series of studies it has, indeed, been possible to reproduce somewhat similar phagocytic phenomena with experimental antinuclear or antinucleoprotein sera (Miescher and Fauconnet, 1954*a*). Furthermore, it could be shown that the absorption of lupus serum with cell nuclei or with nucleoprotein abolished its capacity to induce the L.E. phenomenon (Miescher and Fauconner, 1954*b* ; Miescher, 1957).

In recent years, various groups of investigators have demonstrated that serum from patients suffering from SLE and not yet under the influence of steroid treatment, may exhibit several antinuclear immune reactions, not only with whole nuclei and nucleoprotein, but also with DNA (Cepellini, Polli and Celada, 1957 ; Deicher, Holman and Kunkel, 1959 ; Holman and Kunkel, 1957 ; Miescher and Straessle, 1957 ; Seligman, 1957), histone (Kunkel, in press) and with a water soluble extract of nuclei or of the buffy coat (Holman and Kunkel, 1957). The exact nature of the substance in the extract of nuclei which gives a positive complement-fixation reaction with the serum of some lupus patients has not yet been elucidated ; according to the suggestion of Kunkel it might represent ribose nucleoprotein.

What is the meaning of all these antinuclear immune reactions for the pathogenesis of the disease ?

At first glance it seems logical to ascribe many of the histological changes present in SLE to the action of these antinuclear substances, because nuclei are present all over the organism and no better explanation could be found to explain the systemic character of this disease. Indeed, a first approach to the experimental demonstration of this hypothesis has been made by German (1958), who produced haematoxylin bodies in the kidneys of rabbits and guinea-pigs by injections of L.E. cells. A critical analysis of this experiment, however, diminishes its apparent significance. Since this author injected a large amount of human L.E. cells prepared *in vitro* directly into the renal artery, one would not be surprised to see the L.E. bodies trapped in the glomeruli of the kidney.

A more physiological experiment has been provided by nature namely, the transplacental passage of the L.E. factor from a diseased mother to her newborn child (Berlyne, Short and Vickers, 1957 ; Bridge and Foley, 1954). Surprisingly, no symptoms of SLE are found in the child. Such babies are perfectly healthy despite the fact that their blood shows a strongly positive L.E. cell phenomenon for a short period of time. *In vitro* absorption experiments may give an explanation of the failure of the LE factor to act as a pathogenic agent *in vivo*, since it is easy to absorb this factor on isolated cell nuclei, but not on living cells (Miescher and Fauconnet, 1954b).

However, as the haematoxylin bodies are among the most characteristic and diagnostic features of the disease to the pathologist, one can hardly deny all specific meaning for the pathogenesis of the disease to this deposit of nuclear material. Theoretically, three possible mechanisms which would correlate haematoxylin bodies with the action of antinuclear antibodies suggest themselves :

(i) Haematoxylin bodies may represent the result of a direct aggression by the antinuclear antibodies on the nuclei of living cells. This hypothesis can be discarded on the basis of the apparent lack of pathogenicity for the newborn child of antinuclear factors transferred across the placenta, as well as other evidence of the inability of living cells to absorb the antinuclear factors.

(ii) The antinuclear factors may react with nuclear material derived from the continuous small-scale destruction of cells which normally occurs in the organisms, to form antigen-antibody complexes ; the latter are trapped in the predilected areas by endothelial cells. The fact that processes which precipitate cell destruction (bacterial infections, sunburn) are prone to provoke an exacerbation of the disease would give support to this hypothesis.

(iii) The basic mechanism of the disease may involve the cell nuclei in a still unknown manner and the antinuclear reactions represent a secondary phenomenon, though somehow connected with the pathogenesis of the disease. A hypothetical primary pathological nuclear process would thus lead to the

formation of haematoxylin bodies and the reaction with the antinuclear antibodies would represent a secondary phenomenon.

In order to investigate this problem more directly we performed a series of experiments : we immunized 6 rabbits and 40 guinea-pigs with cell nuclei and with nucleoprotein, derived from Brucella and from calf thymus, for a prolonged period (the first two injections were with Freund's complete adjuvant). The rabbits succumbed to a Pasteurella epidemic after one month of treatment so that this series could be evaluated only with respect to the serological response of the animals. The guinea pigs have been immunized for more than 3 months and one group is still under continued immunization. The guinea pigs were bled regularly at weekly intervals and the sera tested for direct L.E. phenomenon and for serological reactions with nucleoprotein, desoxyribonucleic acid (DNA), histone and homologous nuclei. One group of 5 animals was treated after 3 months of immunization with 3 intravenous injections of homologous nuclei at weekly intervals followed by two more intravenous injections at daily intervals. After this procedure these animals were sacrificed for histological studies.

During the course of this experiment, a considerable number of animals exhibited positive serological reactions against DNA, nucleoprotein, histone and homologous nuclei, in titres as high as those given by strongly positive sera from patients suffering from SLE (Table I). The strongly positive sera against DNA (calf thymus DNA from Mann Lab., New York, with less than 1% protein) were tested in the complement-fixation reaction against DNAse-treated DNA, with negative results, which indicates that the serological response is dependent on the integrity of the DNA molecule.

TABLE I.—*Results of Serological Reactions in 29 Guinea Pigs Immunized with Cell Nuclei or Nucleoprotein.*

	Complement fixation test. (Antigen used in test.)			
Antigen used in test.	DNA (calf thymus).	Guinea pig nuclei.	Histone (calf thymus).	Direct L.E.-phenomenon.
Number positive . .	7	16	8	1 (weak)

The sera of two rabbits gave a strong positive reaction with nucleoprotein and with guinea pig nuclei, using the fluorescent antibody technique of Coons. These reactions were considerably inhibited by previous incubation of the antigens with the serum of a patient suffering from SLE, showing the similarity of both immune reactions. Similarly, a high incidence of positive results was obtained with the sera of immunized animals by the method of passive cutaneous anaphylaxis (Table II). As in the case of the antinuclear factors in the human disease, a wide cross reactivity of the antinuclear reactions could

be observed; indeed, animals immunized with bacterial nucleoprotein gave positive reactions to calf thymus DNA, salmon sperm DNA and guinea pig nuclei, and animals immunized with calf thymus nucleoprotein or with nuclei derived from various animal species (calf, pig, mouse, sheep) reacted with bacterial nucleoprotein, salmon sperm DNA and guinea pig nuclei.

TABLE II.—*Results of Passive Cutaneous Anaphylaxis with Serum of Rabbits and Guinea Pigs Immunized with Cell Nuclei and Nucleoprotein.*

Number of animals.	Species.	Antigen.	Calf thymus DNA (2 mg./animal).	Brucella nucleoprotein (0·5 mg./animal).
2	Rabbit	Brucella nucleoprotein	1	2
4	,,	Calf thymus	2	2
2	Guinea pig	,, ,,	0	1
11	,, ,,	Cell nuclei	0	8
9	,, ,,	Brucella nucleoprotein	0	9

In contrast to this high incidence of positive reactions, all the tests for the L.E. phomenon were negative with one exception : a guinea pig gave a slightly positive L.E.-like phenomenon. In the guinea pig one has to be careful not to confuse the so-called Kurlow inclusion bodies with L.E. cells. On a morphological basis, however, it is possible to differentiate these two cell forms, and in addition, the Kurlow inclusion body does not stain with the Feulgen technique in contradistinction to the L.E. inclusion body.

Considering the antinuclear antibodies as the pathogenetic pathway of the disease, one might expect that once antibody formation is elicited, the disease would go on by itself. But, interestingly enough, the animals attain a certain antibody titre which has not been exceeded by further immunization. If the immunization procedure is stopped, or if the amount of antigen administered is diminished, the antibody titre decreases. By no means does a self-perpetuating nuclear auto-immunization take place.

The histological examination of the animals has not so far shown evidence of lesions which could be considered as typical for SLE.

These experiments have clearly shown that one can induce experimentally the formation of antibodies against the various antigenic constituents of cell nuclei and that these antibodies do not differ serologically from those in systemic lupus. In one case, it was even possible to obtain in an immunized guinea pig a weak direct positive L.E.-like phenomenon.

There are, however, two main differences between the antinuclear antibodies in SLE and those in the experimental animal groups : it requires very intensive immunization to obtain in animals the formation of antibodies which in the human disease are formed without any obvious and particular antigenic stimulation. Secondly, the L.E. phenomenon which is present in almost all

untreated SLE patients represents a test which is more sensitive than most antinuclear reactions ; in contradistinction, only one of a group of 40 immunized guinea pigs gave a weakly positive L.E.-like phenomenon. This fact cannot be explained merely by the assumption that the antibody does not act against autologous but only against homologous or heterologous nucleoprotein, since the addition *in vitro* of homologous nuclei to the blood of the immunized guinea pigs is not followed by their phagocytosis, in spite of the strongly positive complement fixation reactions with these same homologous nuclei. One might conclude that this obvious, although unexplained, difference between the experimental and clinical antinuclear immune reactions—the inability of the experimental sera to induce the L.E. phenomenon—is responsible for the failure to reproduce typical histological changes. However, patients with SLE and negative L.E. phenomenon are known and, on the other hand, even the guinea pig with a positive L.E.-like phenomenon did not exhibit histological changes typical of SLE.

Whereas these experiments indicate that antinuclear antibodies can be produced by hyperimmunization with nucleoprotein from various sources, including bacterial nucleoprotein, they give no definite answer to the question of the pathogenetic significance of these reactions.

From all these data, one could hardly explain the pathogenesis of SLE as the mere consequence of antinuclear immunization. It seems more probable that the antinuclear antibodies represent a secondary phenomenon of the disease. The haematoxyphilic bodies might well be the consequence of the antinuclear antibodies and the failure to reproduce them in our experimental animals might be ascribed to the brevity of the period of observation.

If one considers the antinuclear antibodies as a secondary phenomenon of the disease, the main problem would concern the triggering mechanism, responsible for initiating and perpetuating the continuous formation of antinuclear antibodies.

The discussion of two aspects might be helpful in answering this question : first, the incidence of antinuclear reactions in conditions other than SLE, and second, the genetic aspects of SLE.

(i) Experience so far has shown a significant incidence of antinuclear reactions in the following conditions, besides SLE : Apresoline disease, rheumatoid arthritis, scleroderma, dermatomyositis, lupoid hepatitis.

Apresoline disease is an unexplained pathological condition, very similar to SLE with the difference that it is not self-perpetuating, but stops after withdrawal of the drug. There is much controversy about the pathogenesis of this disease and attempts to reproduce it in experimental animals have not given conclusive results.

In scleroderma and dermatomyositis, the data on positive antinuclear reactions are scanty, so that it is premature to draw any conclusion.

Lupoid hepatitis represent a special group which is possibly closely related to SLE.

With respect to rheumatoid arthritis, sufficient numbers of patients have been studied by many observers to establish the presence of antinuclear reactions in about 5 to 20% of patients. Table III shows the result of sero-

TABLE III.—*Antinuclear Serological Reactions in SLE, Rheumatoid Arthritis and Miscellaneous Conditions.*

	Complement fixation test with :			
	DNA.	Nucleoprotein.	Histone.	L.E. phenomenon.
SLE	12* (34)†	20 (34)	5 (19)	33 (34)
Rheumatoid arthritis	6 (47)	7 (47)	2 (37)	5 (47)
Uncomplicated	2	2	1	2
RA + SLE	1	3	1	3
Felty syndrome	3	2	0	0
Miscellaneous	1 (65)	2 (65)	3 (65)	0 (65)
Macroglobulinaemia	1	0	0	0
Hepatic cirrhosis	0	1	1	0
Multiple myeloma	0	1	0	0
Pneumonia	0	0	1	0
Pyelonephritis	0	0	1	0

* Number of positive results.
† Total number investigated, in parentheses.

logical tests in our own patients seen in Bellevue Hospital : the complement fixation test with DNA and nucleoprotein in the SLE group gives a relatively low incidence of positive reactions. This is due to the fact that most patients were on steroid therapy at the time of testing which considerably lowers the incidence and titre of these immune reactions.

The examination of our group of rheumatoid arthritis patients brings out two interesting points.

(*a*) Three patients developed symptoms consistent with SLE after a typical and long course of rheumatoid arthritis with positive SCA tests, so that the final clinical diagnosis was SLE. All three had positive LE cell phenomena and positive serological reactions with nucleoprotein. Some authors would consider the history of arthritis as the first manifestation of SLE, but if the clinical picture has been typical of rheumatoid arthritis for many years, with marked deformities of the involved joints and with subcutaneous nodules, and with no symptoms of visceral involvement, we think it would be an over-simplification of the problem to regard the whole disease as SLE.

(*b*) Among patients with rheumatoid arthritis, those with Felty's syndrome had the highest incidence of antinuclear reactions. Of four patients with Felty's syndrome, three exhibited positive antinuclear reactions.

What conclusion can be drawn from the striking incidence of antinuclear reactions in rheumatoid arthritis and from the fact that a small number of

patients with rheumatoid arthritis finally develop SLE ? Some authors have suggested that both conditions belong to the same nosological entity. Others have tried to resolve this problem by considering a patient with antinuclear reactions as suffering from SLE, regardless of the clinical findings. We cannot join either of the two groups. As the antinuclear reactions seem to represent a secondary though highly characteristic immune response in SLE, the presence of these reactions does not prove the presence of SLE. Otherwise all our experimental animals with positive antinuclear reactions should be considered as suffering from this disease.

To define the difference between rheumatoid arthritis and SLE on an etiological and pathogenetic basis is impossible, as we know nothing definite about the etiology and pathogenesis of either disease. One approach, however, seems to suggest an answer to the question of the relationship which exists between these two conditions. Discoid lupus and SLE seem to belong, as we have already indicated, to the same nosological entity. If there were no fundamental difference between the pathogenesis and etiology of rheumatoid arthritis and SLE, one should expect as high an incidence of pre-existing discoid lupus in the histories of patients with rheumatoid arthritis as in SLE, which is obviously not the case. On the contrary, the coexistence of rheumatoid arthritis and discoid lupus is rare. It would therefore appear likely that rheumatoid arthritis is a separate nosological entity which, however, has some features in common with SLE. Considering the three conditions discoid lupus, SLE and rheumatoid arthritis, we would propose the following schema to represent their respective relationship (Fig. 1). On the one hand, chronic discoid lupus represents only one part of SLE. A still unknown additional mechanism is necessary for the development of SLE. It is not improbable that the antinuclear reactions are connected with this unknown mechanism. Rheumatoid arthritis, on the other hand, represents a separate nosological entity with a pathogenetic mechanism which is very close to that responsible for SLE.

(ii) The genetic aspects open another door for the understanding of the pathogenesis of lupus erythematosus. Leonhardt (1957) summarized the literature and reported the observation of a family with 14 siblings, 5 of whom showed high gamma-globulins without symptoms of disease ; 2 had systemic and 1 had discoid lupus erythematosus with the possibility of dissemination. The fact of a familial incidence of this disease suggests that a particular predisposition is needed to contract lupus erythematosus and in that particular family the predisposition seemed to be manifested by an overproduction of gamma-globulins.

The observed relationship between rheumatoid arthritis and SLE and the genetic aspects of SLE may thus give some suggestions with respect to the trigger mechanism for the development of the peculiar immunereactions in

SLE. The common denominator in both situations is an increase of the serum gamma-globulins. In rheumatoid arthritis, the tendency to form increased amounts of gamma-globulins seems to be acquired ; in the case of the family with a high incidence of hypergammaglobulinaemia, this condition is probably inherited. It might thus be concluded that a predisposition to hyperactivity of the antibody forming system which is either inherited or acquired might enable an otherwise weak antigenic stimulation to provoke a series of immunological phenomena.

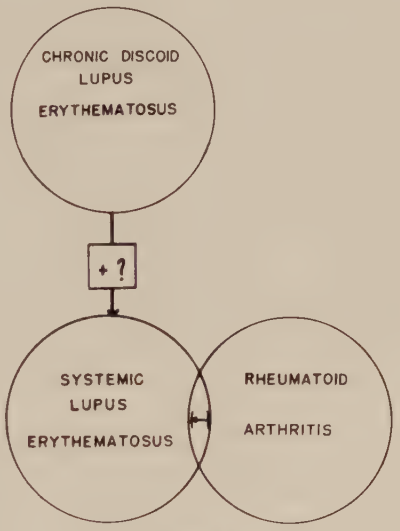

Fig. 1.

Implications for the Pathogenesis of Chronic Discoid Lupus Erythematosus.

The analysis of immune reactions in SLE has not given enough information to understand the pathogenesis of this disease ; however, we have learned that SLE represents a condition with a high tendency to form antibodies, particularly against nucleoprotein, an ubiquitous antigen, also present in the form of bacterial and viral nucleoprotein. In this connection, bacteria of the endotoxin-group might be of primary importance, as endotoxin is known to be an excellent adjuvant for antibody formation. As a matter of fact, whereas it has been impossible in our hands to obtain an antibody response to calf thymus nucleoprotein without Freund's adjuvant, Phillips *et al.* (1958) obtained a considerable antibody response with a crude preparation of Brucella nucleoprotein, which might have contained endotoxins.

In chronic discoid lupus these immune reactions are not present, but the first step toward SLE is present ; therefore from the various immune reactions

in SLE, indirect conclusions with respect to the pathogenesis of discoid cutaneous lupus erythematosus might be suggested.

Cutaneous lupus erythematosus is a pathological condition of the skin commonly restricted to areas which are exposed to sunlight. The role of sunlight seems evident not only from this peculiar localization, but also from the fact that sunlight usually provokes an exacerbation of the disease. Consequently, we must ascribe an important role to sunlight in the pathogenesis of this disease. If we are dealing with an abnormal immune response, as we have suggested for SLE, the following suggestion seems logical. Under the influence of sunlight, the antigenic configuration of a skin constituent is altered so that the organism can be sensitized against it. The process might remain restricted to such a mechanism or, in a few cases with a higher degree of hyperreactivity of the antibody forming system, extend to a generalized immune response in which heterologous nucleoprotein might play a role.

In order to investigate this problem, two suggestions might be proposed, first, to investigate the action of sunlight (or U.V.L.) on the antigenicity of known antigens and second, to test a group of patients with discoid lupus for their ability to form antibody and to develop the delayed type of hypersensitivity and to compare the results with those obtained in a control group.

References.

Berlyne, G. M., Short, I. A. and Vickers, C. F. H. (1957) *Lancet*, ii, 15.
Bridge, R. G. and Foley, F. E. (1954) *Amer. J. med. Sci.*, **227**, 1.
Callender, S. T. and Race, R. R. (1946) *Ann. Eugen., Lond.*, **13**, 102.
Capelli, E. (1952) *Minerva derm., Torino*, **27**, 108.
Cepellini, R., Polli, E. and Celada, F. (1957) *Proc. Soc. exp. Biol., N.Y.*, **96**, 572.
Deicher, R. G., Holman, H. R. and Kunkel, H. G. (1959) *J. exp. Med.*, **109**, 97.
German, J. L. (1958) *Ibid.*, **108**, 179.
Holman, H. R. and Kunkel, H. G. (1957) *Science*, **126**, 162.
Klemperer, P., Gueft, B., Lee, S. L., Leuchtenberger, C. and Pollister, A. W. (1950) *Arch. Path.*, **49**, 503.
Kunkel, H. G. (1957) *Ciba Foundation Symposium on the Cellular Aspects of Immunity*. London: Churchill, in press.
Leonhardt, T. (1957) *Lancet*, ii, 1200.
Marmont, A. (1952) *Schweiz. med. Wschr.*, **82**, 111.
Miescher, P. (1957) *Hautarzt*, **8**, 502.
——— and Fauconnet, M. (1954*a*) *Schweiz. med. Wschr.*, **84**, 1036.
——— ——— (1954*b*) *Experientia*, **10**, 252.
——— ——— and Béraud, T. (1953) *Exp. Med. Surg., Basel*, **11**, 173.
——— and Straessle, R. (1957) *Vox Sang., Basel*, **2**, 283.
——— ——— (1959) *First International Symposium on Immunopathology*. Basel: Benno Schwabe, p. 454.
——— and Vorlaender, K. O. (1957) *Immunopathologie in Klinik und Forschung*. Stuttgart: Georg Thieme, p. 494.
Philips, J. H., Braun, W. and Plescia, O. J. (1958) *J. Amer. chem. Soc.*, **80**, 2710.
Seligmann, M. (1957) *C. R. Soc. Biol., Paris*, **245**, 243.
——— (1959) In *First International Symposium on Immunopathology*. Basel: Benno Schwabe, p. 402.
Ziff, M., Esserman, P. and McEwen, C. (1958) *Arthritis and Rheumatism*, **1**, 332.

PROGRESS IN THE UNDERSTANDING OF LUPUS ERYTHEMATOSUS.*

STEPHEN GOLD, M.D., F.R.C.P.

St. John's Hospital for Diseases of the Skin and
the Institute of Dermatology, Lisle Street, London, W.C. 2.

The term lupus appears to have come into use in the thirteenth century and the disease is said to have been so named because it ate away the part with rapidity or devoured it like a wolf. Bernard de Gordon in 1305, more than six hundred and fifty years ago, described in the *Lilium medicinae* (Skinner, 1949) a corrosive ulcer given the name lupus. Daniel Turner (1714) in his *Treatise of Diseases Incident to the Skin*, speaking of cancer and carbuncle, described small rounded tubercles "*noli me tangere*, or don't meddle with me"—"if it seize upon the Legs and Thighs, it is termed *Lupus*, the Wolf; for that it is, say some, of a ravenous Nature, and like that fierce Creature, not satisfy'd but with Flesh".

It is apparent that for many years the term lupus was used somewhat indiscriminately for ulcerative and mutilating skin conditions, a great many of which must surely have been cancerous. So, after 1827, when Jacob described rodent ulcer, the condition called lupus vulgaris by Willan as early as 1800 became more clearly defined. Things were further simplified by Koch's discovery of the tubercle bacillus in 1882. So far as the erythematous variety is concerned, 1827 seems to be its birthdate when Rayer recognized it and christened it fluxus sebaceus. Some of the other names used in the early days are given in Table I, but I am sure that as many again can be discovered by a full search through early papers. Cazanave (1851) takes the credit for

Table I.—*Early Names for Lupus Erythematosus.*

Fluxus sebaceus	(Rayer, 1827)
Érythème centrifuge	(Biett, 1828)
Seborrhoea adultorum	(Fuchs, 1840)
Seborrhoea congestiva	(Hebra, 1845)
Lupus erythematosus	(Cazenave, 1851)
Herpès crétacé	(Devergie, 1854)
Erythema lupinosum	(Veiel)
Vespertilio	(Squire)
Ulerythema centrifugum	(Unna)

evolving the name which subsequently found favour, in spite of the fact that the word erythematosus, half Latin and half Greek, is a hybrid.

Having thus been clearly identified from a clinical standpoint, its nature

* This paper was read at a Symposium on Chronic Discoid Lupus Erythematosus held by the Section of Dermatology of the Royal Society of Medicine on 21 May, 1959.

was the subject of a debate at the International Congress of Medicine in London in 1881. Kaposi had much to contribute, but it is fair to say that opinion was divided at the conclusion, though many agreed that it was a peculiar type of inflammation not starting in the sebaceous glands.

The next stage of the story is set in 1872, when Kaposi described the acute variant. In his first two publications he stressed the stormy course, its predilection for young females and its fatal outcome. He was aware of the joint involvement, lymphadenopathy and anaemia, as well as the various skin eruptions which could be seen. Argument then started as to the relationship between the acute and cutaneous types, an argument which raged for over sixty years. The first acute example recorded in this country was reported by Fagge and Pye-Smith (1891).

For some five decades we read of a long drawn-out and somewhat dreary controversy about the aetiology of this condition. Many advocated that the disease was tuberculous in origin and it would seem that the frequency of finding active tuberculosis at autopsy of fatal cases and the name lupus, which itself has caused and still does cause much confusion in the minds of students, was largely responsible. A little more recently, some stress was placed on the cutaneous reaction these patients produced to various types of tuberculin tests, to support the tuberculous hypothesis, one strongly advocated by Boeck (1898*a* and *b*) Besnier, and Unna. However, around the turn of the century, some sceptical voices were raised, notably those of Koch (1896), Jadassohn (1904) and Sequiera and Balean (1902).

The next decade finds the controversy raging between the tuberculous and toxic theories. Friedlander (1911) from the results of Moro tests, felt that the condition was not due to tuberculosis as such and that the cause was probably some related toxin. Soon after, the concept of hypersensitivity to streptococcol infections was suggested (Barber, 1915).

We may now leave the somewhat sterile and long drawn-out argument concerning aetiology, for other things were arising in what we may call the systemic field. Osler (1895, 1900 and 1904) wrote stimulating papers concerning the widespread visceral manifestations of the acute illness, and George Pernet (1908) described a patient with mitral vegetations some years before the more famous observations of Libman (1917, 1920, 1922 and 1923) and Libman and Sacks (1923 and 1924). During and after the work of Libman and Sacks, Baehr and his colleagues (1935*a* and *b*) studied the vascular changes, particularly those in the kidney. It was they who described the hyaline appearance of the glomerular capillaries as resembling wire loops—a happy phrase that has been assimilated into pathological jargon. Then we come to the giant of them all-Paul Klemperer. He had been working with Baehr at the Mount Sinai Hospital and with Pollack described the connective tissue changes which had hitherto escaped all eyes (Klemperer *et al.*, 1941, 1942*a*

and *b*). These workers made the point that in the systemic illness, whether the tissue affected was skin, vascular endothelium or renal glomerulus, the changes seen were all variations of the same basic pattern, notably fibrinoid degeneration of collagen, with peculiar alteration in the ground substance producing metachromasia. The cellular changes were limited to the fibroblasts, which showed both proliferation and degeneration.

We find that at this time, the Cinderella of the story, the original and more common cutaneous type of the disease, was falling into the background. In fact, the relationship between the cutaneous and systemic forms, if not in jeopardy, was certainly suspect; for there were now many suggestions that these two were separate conditions only related by chance association.

Yet further steps were made in the understanding of the systemic illness, particularly after the identification and interpretation of the L.E. cell, first described by Hargraves, Richmond and Morton (1948), around which a vast literature has developed. It is from this observation that many immunochemical investigations have stemmed and the chemical basis of this reaction may prove to be the linchpin of the whole disorder. Next came ACTH and various steroid hormones, which though not revolutionizing the outlook in the systemic illness, have at least materially influenced its couse. Finally, it was recognized that widespread disturbance of the body's immune mechanism as a whole occurred in this disease, with a tendency to develop autoantibodies not only to the cellular elements of the blood, to account for anaemia, leucopoenia and thrombocytopoenia, but probably also to fixed tissues and vascular endothelium as well (Dameshek, 1958).

Cinderella crept back into the limelight, however, when it was suggested that in fact many of the cutaneous cases were systemic at the outset, or at least potentially so. The identity of the two manifestations was becoming re-established (Montgomery and McCreight, 1948). Cohen and Cadman (1953) reported a group of cases of which some of the chronic discoid showed a disordered pattern of serum proteins, as well as many haematological abnormalities ; they pointed out that it may be impossible clinically to differentiate types of case. Furthermore, Marten and Blackburn (1956) from careful studies, felt that a large number of patients with chronic discoid disease showed not only the presence of L.E. cells, but also other abnormalities, such as a raised sedimentation rate, leucopoenia, and anaemia. Another investigation by Dubois and Martell (1956) showed that the majority of the so-called cutaneous cases not only had systemic changes as shown by laboratory tests, but also clinical features which suggested systemic involvement.

It would seem that the classification to which we had become accustomed is now becoming invalid as a result of these more careful investigations of patients and it was with this in view that I interested myself in a group of patients at St. John's Hospital for Diseases of the Skin over the last three or four years.

The number of new patients diagnosed as suffering from lupus erythematosus compared with the total number of new patients seen in each of seven consecutive years, is given in Table II. It is remarkable to see how closely these figures

TABLE II.—*The Number of Cases of Lupus Erythematosus Seen in Seven Consecutive Years.*

	1952	1953	1954	1955	1956	1957	1958
Total number of new patients .	20,427	19,404	17,771	16,680	15,512	14,960	13,886
Discoid L. E.	136	133	118	73	82	64	46
Systemic L. E.	3	2	6	5	8	1	2
All L. E.	139	135	124	78	90	65	48

compare with those of fifty-five years ago, when Radcliffe-Crocker reported that of ten thousand new patients seen in one year, sixty-three had discoid lupus erythematosus. Gahan (1942) showed that so far as European stock was concerned, the incidence of lupus erythematosus is approximately the same in whatever part of the world the patients may live. Quite different from skin cancer, for instance.

Of the one hundred and seven patients analysed in this series, five were discarded on diagnostic grounds and two seemed obviously systemic cases on quite superficial questioning. Of the remaining one hundred patients, sixty-one were female and thirty-nine were male. Their age of onset is given in Fig. 1.

With the exception of two Cypriots, one West Indian, and one Anglo-Indian, all males, the patients were from this country. The notes revealed only three initial mistakes in the original diagnoses, viz., rosacea, seborrhoeic dermatitis and eczema. The great majority of cases were of the discoid scarring variety, and several were of the labile, superficial type showing minimal scarring. In six patients, the disease was confined to the scalp, and three cases were of the chilblain variety. The distribution on the head and neck is shown in Table III. It is noteworthy that in males, involvement of the ears was relatively common.

TABLE III.—*Sites Involved.*

	Female.	Male.
Nose	38	15
Cheeks	32	25
Scalp	11	11
Forehead	9	5
Ears	8	18
Neck	5	6
Peri-orbital . . .	4	3

Males complained more often of local symptoms and in both sexes itching and burning were the most frequent. Sunlight was easily the most frequent aggravating factor, with heat, emotional upsets and cold following in that order. In women, the rash was worse at the menses in five of sixty-one, and better in two ; pregnancy definitely helped the rash in three of sixty-one and did not influence it in two. Of these sixty-one females, seven complained of arthralgia, fourteen had had severe chilblains and eleven noted dead fingers in cold weather ; three had suffered from some type of drug reaction.

These patients were all subjected to the same laboratory investigations, which included a full blood count, sedimentation rate (Westergren), analysis of urine, search for L.E. cells and examination of serum protein pattern by electrophoresis,

as well as Rose-Waaler and Coombs tests. The Rose-Waaler and Coombs tests were negative in the full one hundred patients. The sedimentation rate was raised about 15 mm. in thirteen of sixty-one females and of these, twelve revealed an abnormal serum protein pattern. Of the males, only two out of thirty-nine had a sedimentation rate above 10 mm. One man had a grossly disturbed serum protein pattern, a florid labile rash and arthralgia, but L.E. cells were never found. Only one patient of this whole series revealed L.E. cells, a women with two chronic fixed discoid patches; she would not have been suspect on clinical grounds. Her sedimentation rate was never over 20 mm., but the gamma-globulin level was grossly raised and

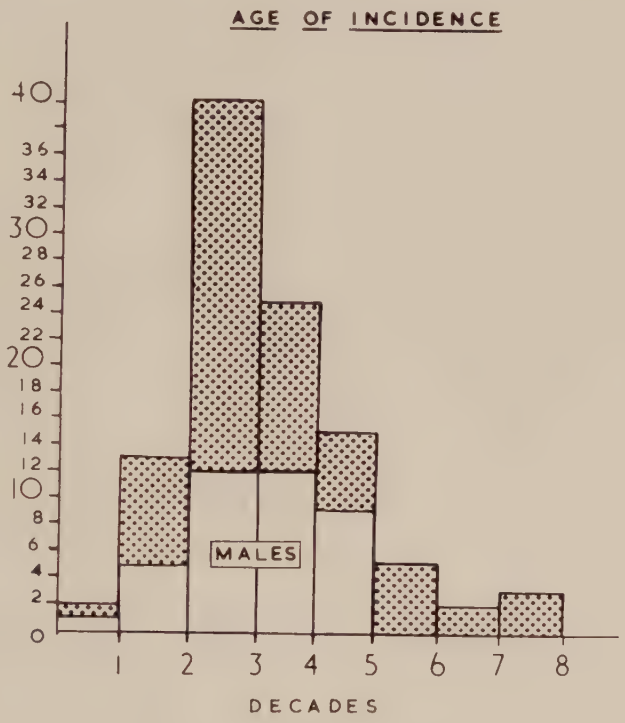

Fig. 1.

she responded dramatically to chloroquine administration. Another old lady of seventy-two showed many systemic features, including cryoglobulinaemia, leucopoenia and a sedimentation rate of over 50 mm., as well as a labile skin rash, but L.E. cells were never found.

The results of serum protein analyses showed that 39% of these patients had some deviation from normal—twenty-five of sixty-one females and fourteen of thirty-nine males (Table IV). The most common abnormality was simply a raised level of gamma-globulin, the next being a simple increase of the beta fractions. After that came various combinations and permutations. One cannot readily draw conclusions from these findings, though we may note that a gross increase of gamma-globulin of over 2 g. is probably significant. At the moment, one is not in a position to say what is the upper limit of normal for these various protein fractions in patients with other skin diseases.

TABLE IV.—*Abnormal Serum Globulins.*

Standard α_1- up to 0·3 g. α_2- up to 0·8 g.
β- up to 0·9 g. γ- up to 1·4 g.

25 Females :			
14 had increased		γ-	globulins.
4	,,	,, β-	,,
1	,,	,, β- + γ-	,,
1	,,	,, α_1- + β-	,,
1	,,	,, α_2- + β-	,,
1	,,	,, α_1, α_2-, β- + γ-	,,
1	,,	,, α_1-, β- + γ-	,,
1	,,	,, α_1- + γ-	,,
1	,,	,, α_1-, α_2- + β-	,,
14 Males :			
8 had increased		γ-	globulins.
1	,,	,, α_1- + α_2-	,,
3	,,	,, β-	,,
1	,,	,, α_2-, β- + γ-	,,
1	,,	,, β- + γ-	,,

So far as blood counts are concerned, I have not attempted to analyse these in any detail. The total white count was frequently below four thousand and mild degrees of hypo- and normochromic anaemia were commonly seen. In this respect my findings are in close agreement with those of Cohen and Cadman (1953) and Marten and Blackburn (1956). However, I did not find L.E. cells as frequently as the latter authors and my patients did not reveal the symptoms of the systemic illness as frequently as was reported by Dubois and Martell (1956).

All these findings bear out the suggestion that cases of the chronic cutaneous types of the disease often show signs of a disturbance of body mechanisms more gross than was realised twenty years ago. These facts should not, I think, make us any more cautious in our treatment or pessimistic in our prognosis. There is nothing to suggest that a greater percentage of patients in the cutaneous group passes into the frankly systemic illness than before and many of those who do reveal laboratory signs of systemic disturbance will come to terms with their skin disease, live a healthy existence and probably die of something entirely different.

Turning to therapy of the condition, though based throughout on empirical observations, the most important phase of progress was the recognition of the value of antimalarial compounds. In 1894, J. F. Payne described the use of quinine in febrile states for he noted that a marked pallor developed as a result of its use. Soon after, this drug was used in lupus erythematosus, and was often accompanied by the application of tincture of iodine to the diseased patches, as advocated by Hollander in the earlier decades of the century. More recently, quinine has been replaced by other preparations, notably mepacrine, first suggested by Prokoptchouk (1940) and used by Sorinsen (1941), Popoff and Kutinscheff (1943). Independently, Page (1951) at the Middlesex Hospital recounted the successful use of mepacrine and it was really through

his paper that the drug was accepted and used in the Western world. Since then a number of reports have supported Page's original claim, pointing out, however, the disadvantages of treatment with mepacrine, notably the yellow discoloration of the skin, the development of lichenoid rashes, occasional blood dyscrasias, central nervous system involvement and ocular disturbances. Soon after the arrival of mepacrine came chloroquine and most recently hydroxychloroquine, compounds chemically and pharmacologically related. These more recent drugs have fewer disadvantages, though the side effects, especially the ocular and gastro-intestinal, are occasionally troublesome. It is fair to say that all practising dermatologists now agree upon the material benefits which these drugs have conferred upon our patients with discoid lupus erythematosus. We have used them long enough to form some definite conclusions.

First, their effect is suppressive and temporary. Disappointingly, patients relapse with regularity when the drug is withheld. Certain clinical types vary in their response, for instance, those with scalp involvement are slow to respond, though in any event, I find that lupus erythematosus on this site is notoriously resistant. The benefit provided by the antimalarials is not confined to cutaneous cases, for sometimes they seem to be effective in the systemic. It has been suggested, for instance, that some patients are controlled on a smaller amount of systemic steroids if at the same time chloroquine is administered. I have no personal observation to make on this claim.

Of a group of patients in whom the disease appears to be more than cutaneous, speaking symptomatically rather more than on the results of laboratory tests, I can recall three or four who have been impressed by the degree of recovery of energy and appetite, relief of arthralgia, as well as a great improvement in their general wellbeing, as a result of taking chloroquine. We are, of course, aware of the beneficial effects that this drug has on patients with rheumatoid arthritis. At the moment, there is not enough information to do more than speculate about the mode of action of these drugs. We can be sure that they do not have a steroid-like action, nor does their suppressing effect on light sensitivity explain the beneficial results obtained. There are two observations made recently which give rise to thought. It has been shown that the L.E. cell phenomenon *in vitro* can be blocked by the addition of mepacrine to the system (Holman and Kunkel, 1957). Furthermore French reports about the good response of discoid lupus erythematosus to the intralesional injections of a solution of chloroquine, if confirmed, suggest that this mode of treatment may be more useful in those patients who are intolerant of the drug when given systemically (Calas and Castelain, 1958).

The facts about response to chloroquine in my hundred patients can briefly be stated. Eighty per cent improved, indeed, 20% cleared, but the relapse rate was disquietingly high when the drug was stopped. Occasionally, one

preparation seemed to be more successful than another, nevertheless, there remained a hard core of some 20% of patients who were resistant to treatment. Analysis of the serum protein patterns of those who responded and those who were resistant to the drug provided no fruitful information. Side effects produced by chloroquine, for this was the drug most extensively used, were largely gastrointestinal (anorexia and nausea), visual (blurring of vision and diplopia) headache and giddiness in that order. Females seemed more prone to side effects than males. There were two examples of leucotrichia, two patients developed leucopoenia, and one male patient developed an erythema multiforme type of reaction.

Discussion.

It may reasonably be argued that most recent advances have been made in respect of the systemic illness, but I believe that the recognition of the essential unity of systemic and cutaneous lupus erythematosus is a major step forward. The cutaneous disease is but a benign variant of the systemic, in which the disease process, for some curious reason, remains a localized tissue reaction. Current feeling suggests that we are dealing with a change in a skin already susceptible, akin to the Koebner phenomenon. There have been many reports of localized lupus erythematosus following injury of the skin, burns, or even infection. Possibly sunburn is but a type of trauma causing a susceptible skin to undergo the reaction. Mechanical trauma in the mouth, friction on the scalp may start the change, though one must stipulate that the tissue is already in a receptive state. Careful testing with a monochromator by Magnus (1959) at the Institute of Dermatology has shown that patients with lupus erythematosus, even those appearing to be sun sensitive, in fact do not react abnormally to any specific light band. He has thus confirmed the work of Rottier (1959) in Holland. This is different from the results in a group of patients suffering from polymorphic light eruption, who produce abnormal reactions to such tests. The fact is impressive that these patients are not sun sensitive in the ordinary sense, but sunlight, like mechanical trauma and cold, is able to initiate this curious change in a skin already in a receptive condition, as in eruptive psoriasis or lichen planus. We may note the remarkable effect that the antimalarial drugs have on the skin lesions, as well as on some of the systemic features. Their mode of action has yet to be established, but nevertheless, their interference with the formation of L.E. cells gives food for thought. We would do well, however, to heed the words of Dr. G. B. Dowling (1954) who only five years ago wrote that " those who have done most work on this subject have been the least prepared to speculate upon the pathogenesis and aetiology of the disease ". Immunological and cytochemical studies will help to unravel this peculiar and fascinating process.

I would like to thank my clinical colleagues at St. John's Hospital for Diseases of the Skin for referring the patients to me. I would also like to thank Dr. J. O. Oliver, Director of Pathology, and particularly Dr. Arthur Tickner and Mr. R. C. Syms for undertaking the many arduous laboratory investigations without which this paper would be meaningless.

References.

Baehr, G., Klemperer, P. and Schiffrin, A. (1935*a*) *Trans. Ass. Amer. Phycns.*, **50**, 139.
——— ——— ——— (1935*b*) *Amer. J. Path.*, **2**, 881.
Barber, H. W. (1915) *Brit. J. Derm.*, **27**, 365.
Boeck, C. (1898*a*) *Arch. Derm. Syph., Berlin*, **42**, 87.
——— (1898*b*) *Brit. J. Derm.*, **10**, 371.
Calas, E. and Castelain, P. Y. (1958) *Presse méd.*, **66**, 1219.
Cazenave, C. (1851) *Ann. Mal. Peau*, **3**, 298.
Cohen, H. and Cadman, E. F. B. (1953) *Lancet*, ii, 305.
Dameshek, W. (1958) *Ann. int. Med.*, **48**, 707.
Dowling, G. B. (1954) *Practitioner*, **173**, 140.
Dubois, E. L. and Martel, S. (1956) *Ann. int. Med.*, **44**, 482.
Fagge, C. H. and Pye-smith, P. H. (1891) *Textbook of the Principles and Practice of Medicine*, London : J. and A. Churchill, Vol. II, p. 916.
Friedlander, D. (1911) *J. cutan. Dis.*, **29**, 417.
Gahan, E. (1942) *Arch. Derm. Syph., Chicago*, **45**, 685.
Hargraves, M. M., Richmond, H. and Morton, R. (1948) *Proc. Mayo Clin.*, **23**, 25.
Holman, H. R. and Kunkel, H. G. (1957) *Science*, **126**, 162.
Jadassohn, J. (1904) in Mraček's *Handbuch der Hautkrankheiten*. Vienna : Alfred Hölder, vol. III, p. 298.
Kaposi, M. (1872) *Arch. Derm. Syph., Berlin*, **4**, 36.
Klemperer, P., Pollack, A. D. and Baehr, G. (1941) *Arch. Path., Chicago*, **32**, 569.
——— ——— ——— (1942*a*) *J. Amer. med. Ass.*, **119**, 331.
——— ——— ——— (1942*b*) *N.Y. St. J. Med.*, **42**, 2225.
Koch, F. (1896) *Arch. Derm. Syph., Berlin*, **37**, 39.
Libman, E. (1917) *Med. Clin. N. Amer.*, **1**, 573.
——— (1920) *Brit. med. J.*, ii, 304.
——— (1922) *Trans. Ass. Amer. Phycns.*, **37**, 233.
——— (1923) *J. Amer. med. Ass.*, **80**, 813.
——— and Sacks, B. (1923) *Trans. Ass. Amer. Phycns.*, **38**, 46.
——— ——— (1924) *Arch. intern. Med.*, **33**, 701.
Marten, R. H. and Blackburn, E. K. (1956) *Arch. Derm., Chicago*, **73**, 1.
Magnus, I. (1959) Personal communication.
Montgomery, H. and McCreight, W. G. (1949) *Arch. Derm. Syph., Chicago*, **60**, 356.
Osler, W. (1895) *Amer. J. med. Sci.*, **110**, 624.
——— (1900) *Brit. J. Derm.*, **12**, 227.
——— (1904) *Amer. J. med. Sci.*, **127**, 1.
Pernet, G. (1908) *Thèse de Paris*, Rousset, Paris.
Page, F. (1951) *Lancet*, ii, 755.
Popoff, L. and Kutinscheff, M. (1943) *Derm. Wschr.*, **116**, 186.
Prokoptchouk, A. J. (1940) *Vestn. Vener. Derm.*, **2/3**, 1940, *cit. Zbl. Haut.-u. GeschlKr.*, **66**, 112.
Rottier, P. B. (1959) Personal communication.
Sequeira, J. H. and Balean, H. (1902) *Brit. J. Derm.*, **14**, 367.
Skinner, H. A. (1949) *Origin of Medical Terms*. London : Baillière, Tindall and Cox.
Sorinson, N. S. (1941) *Vrach. Dyelo.*, **23**, 441.
Turner, R. D. (1714) *De Morbis Cutaneis. A Treatise of Diseases Incident to the Skin*. London.

ROYAL SOCIETY OF MEDICINE.

SECTION OF DERMATOLOGY.

President—Professor J. T. Ingram.

21 May 1959.

A symposium was held on chronic discoid lupus erythematosus. Opening papers by Dr. Stephen Gold and Professor Peter Miescher are published elsewhere in this issue.

Lichen Sclerosus with Pigmentary Disturbance.—Dr. E. Wilson Jones (for Dr. H. J. Wallace).

A woman aged 70.

History.—Patient first noticed pigmentation and itching of the skin about 1952. The pigmentation gradually deepened and became particularly prominent on the neck. White patches have appeared in the pigmented areas and have gradually increased in extent and number. The skin has become more irritable in the past six months. General health is good apart from bronchitis and attacks of pneumonia in the past. No previous history of skin trouble or of skin trouble in the family.

Examination.—The patient's skin is generally hyperpigmented except for large geographical areas of white skin. The areas of pigmentation and depigmentation are roughly symmetrical. The depigmented areas show numerous small atrophic lichenoid papules which have a shiny surface. The depigmented skin has lost its normal texture and elasticity. Mouth and vulva are not affected : skin appendages normal. There are scratch marks on the back and buttocks, and also a few superficial follicular pustules on the back. General medical examination—no relevant findings.

Investigations.—Blood count normal. E.S.R. 10 mm. in 1 hour. Chest skiagram : no evidence of recent disease.

Dr. R. T. Brain : I thought it was vitiligo.

Dr. E. Wilson Jones : There are no lesions on the vulva. The histology shows a burnt-out process in the epidermis and is compatible with a diagnosis of lichen sclerosus or superficial scleroderma.

Dr. G. B. Dowling : The vulva is not invariably involved in lichen sclerosus. I think that diagnosis is correct.

The President : I have always felt that there is a close family relationship between alopecia vitiligo and scleroderma, one or other being seen in different members of a family. With an extensive scleroderma of any type you get pigmentation dysfunction. I thought this was lichen sclerosus.

Dr. E. Wilson Jones: It has been associated with vitiligo in a number of patients.

The following cases have been published in *Proc. R. Soc. Med.*, **52**, 1031.

Amblyopia in Lupus Erythematosus.—G. C. Wells, F.R.C.P.

Weber-Christian Disease. ? A Collagen Disease.—M. A. Veitch, M.B. (for C. W. Bartley, D.M., M.R.C.P.).

The following cases also were shown :

Lupus Erythematosus in Grafted Burn Scar.—Dr. E. N. M. Johnston.

Chronic Discoid Lupus Erythematosus.—Dr. M. Feiwel.

Lupus Erythematosus.—Dr. W. Tillman.

? Lupus Erythematosus.—Dr. Bentley Phillips.

Lymphocytoma Cutis.—Dr. J. D. Everall (for Dr. G. B. Mitchell-Heggs.).

Myxoedema Papulosum.—Dr. M. A. Smith (for Dr. Bernard Green).

Hansen's Disease.—Dr. E. N. M. Johnston (for Dr. G. C. Wells).

CURRENT LITERATURE

HEREDITARY HAEMORRHAGIC TELANGIECTASIA AND PULMONARY ARTERIOVENOUS FISTULA. SURVEY OF A LARGE FAMILY. C. H. Hodgson, H. B. Burchell, C. A. Good and O. T. Clagett. (1959) *New Engl. J. Med.*, **261**, 625.

A man died in 1920 leaving 330 descendants. Of these 40% have telangiectasia and more than 6% have pulmonary arteriovenous fistulas. These fistulas are dangerous and should be excised if they are enlarging or if haemoptysis, haemothorax, polycythaemia, abscess formation or infection occur.

The authors think that all members of families with hereditary telangiectasia should have the thorax X-rayed at intervals, whether they have symptoms of fistula or not. A. D. P.

ACQUIRED HAEMOLYTIC ANAEMIA SECONDARY TO BOECK'S SARCOID. W. O. West. (1959) *New Engl. J. Med.*, **261**, 688.

A patient with haemolytid anaemia secondary to splenic involvement in Boeck's sarcoid is described. The anaemia was relieved by splenectomy. A. D. P.

ACUTE LUPUS ERYTHEMATOSUS WITH LARYNGEAL INVOLVEMENT. D. G. Scarpelli, F. W. McCoy and J. K. Scott. (1959) *New Engl. J. Med.*, **261**, 691.

The death from laryngeal oedema of a man with systemic lupus erythematosus is reported. A. D. P.

GREY PIGMENTATION OF SKIN AND MUCOUS MEMBRANES IN PATIENTS TREATED WITH SYNTHETIC ANTIMALARIALS. X. Vilanova and J. M. Mascaró. (1959) *Actas Dermo-Sif., Madrid*, **50**, 309.

Five patients with grey-blue pigmentation of the skin and mucous membranes due to the use of synthetic antimalarials for treating lupus erythematosus are described. The pigmentation fades some months after discontinuation of the drugs. The pigmentation especially involves the palate and at times the buccal mucosa, the ocular conjunctiva and the nail bed. but less often, the body skin, although the anterior surface of the legs may be affected. Histologically there is excess of dermal haemosiderin and melanin within histiocytes. These histiocytes are found in the superficial and middle layers of the dermis, the blue appearance being produced by the deeper cells.

The authors refer to the description of Lutterloh and Schallenberger (*Archive Derm. Syph.*. (1946), **1**, 349) of such pigmentation occurring in 8 patients treated with Quinacrine for malarial prophylaxis ; also to 4 papers by De Graciansky and Grupper in the French literature describing 8 new cases occurring in chronic L.E. treated with chloroquine (Nivaquine). P. M. I.

CONTRIBUTION TO THE STUDY OF IDIOPATHIC HAEMORRHAGIC PIGMENTED SARCOMA OF KAPOSI. R. González Medina, Emilio Alcalá and Ramón González Fontana., (1959) *Actas Dermo-Sif., Madrid*, **50**, 315.

Kaposi's sarcoma in a man aged 39 is described. There was radiographically enlargement of the sella turcica with anterior clinoid destruction. Various treatments given included courses of synthetic steroids of Prednisone and Prednisolone type supplied as a proprietary preparation. To the steroid courses were later added penicillin. Appreciable lesional modification was obtained but the result was not so good as has been claimed for ACTH.

In summary a more or less general alteration of the mesenchymal layer and especially of the capillaries is postulated. In view of the pituitary tumour a hypothalamic pituitary block is considered possible as the cause of the disorder. P. M. I.

COMPARATIVE STUDY OF METHODS OF CONSERVING FUNGUS CULTURES. Manuel Pereiro Miguens. (1959) *Actas Dermo-Sif., Madrid*, **50**, 347.

Various methods of preserving fungus cultures are compared and the method described by Negroni is found the best. The cultures are preserved by drying in phosphoric acid vapour. Of a large number of fungi preserved for nine years in this way only one (*M. canis*) could not

be re-sown to produce normal macroscopic and microscopic characteristics of the organisms concerned. The method is described thus :

A small tube sealed with cotton wool containing the fungus culture is inserted into an ordinary test tube in the end of which has been introduced a little anhydrous phosphoric acid. Above the acid a rod of glass prevents the fungus containing small tube from contacting the acid. The end of the ordinary test tube is then drawn out by a blow pipe and connected with the rubber tube of a vacuum pump. After 2 or 3 minutes of pump action the test tube is sealed by a flame at its drawn out end. The author claims fungus preservation for many months by this method. When it is desired to re-grow the fungus the test tube is broken and the smaller contained tube withdrawn and its contents transplanted on to the ordinary media. P. M. I.

CARCINOMA OF THE SKIN. H. Gordon. (1959) *Practitioner*, **182**, 719.

The clinical varieties of basal-cell carcinomata and squamous-cell epitheliomata are described and the importance of settling the differential diagnosis of any doubtful lesion is emphasized. The twin pillars of treatment are radiotherapy and surgery.

Molluscum sebaceum is now well recognized and, although spontaneous resolution occurs within three or four months, the process may be unsightly, and leave a slight and often depressed scar. If there is any doubt about the diagnosis a biopsy should be done, and excision, or planing the lesion and cauterization avoids a disfiguring scar.

Malignant melanoma should be suspected when there is an increase of pigmentation in a pre-existing mole or pigmented macule. Once the diagnosis is established the treatment is entirely surgical.

Pre-cancerous conditions include senile keratosis, pitch wart, lentigo maligna, Bowen's disease, Paget's disease of the nipple, erythroplasia of the penis and possibly xeroderma pigmentosum. R. J. C.

BLEACHING OF THE HAIR, UNUSUAL ACCIDENT IN TREATMENT WITH COLOURLESS SYNTHETIC ANTIMALARIALS. Gh. Speranţă. (1958) *Derm. Ven., Bucharest*, **4**, 351.

A nursing sister aged 39 with discoid lupus erythematosus treated unsuccessfully for 9 years (atebrine included—no details) improved satisfactorily in 1956 with aralen. Giddiness on bending present in the first 10 days while on 2 tablets daily, disappeared with reduction of dosage to 1 tablet. The patch had greatly improved but the hair for a distance of 1 cm. from the skin had become blonde—noticeable from a distance (axillary and pubic hair similarly affected). Pigmentation present over part of the lupus erythematosus patch had become much less. With continuation of treatment for 10 days the decoloration had become accentuated and continued for 3 weeks after cessation of treatment—now 3–4 cm. : the eyebrows nearly white with some normal hairs. Relapse on suspending treatment. Reported 4 months after suspension of treatment with active lupus erythematosus and normal hair colour. M. S. S.

PIGMENT FORMING TRICHOPHYTON MENTAGROPHYTES IN GUINEA-PIG TRICHOPHYTOSIS. H. Langer. (1959) *Derm. Wschr.*, **139**, 621.

A trichophyton epidemic in guinea-pigs is described. *T. mentagrophytes* was grown in every case, and showed intensely red pigment formation. The same feature was evident on culture from human contacts. The typical appearance of the culture on different media as well as the micro-morphology made the differential diagnosis from *T. rubrum* a certainty. J. M.

BIOCHEMICAL RESEARCH ON THE SKIN. S. Rothman. (1959) *Derm. Wschr.*, **139**, 643.

The discovery of squalene in the human skin has given a considerable impetus to research of the synthesis of cholesterol. Various skin cells of mammals have enzyme systems that are connected with cholesterol synthesis. The skin is, therefore, particularly suitable for investigating this problem. J. M.

TREATMENT OF SUPERFICIAL TRICHOPHYTOSIS OF SCALP AND BODY WITH GRISEOFULVIN. J. Tappeiner. (1959) *Derm. Wschr.*, **140**, 744.

A girl aged 4, daughter of a dermatologist, developed ringworm of the face and scalp. The source was traced to an infected guinea-pig. *T. mentagrophytes* was cultured. She responded well within eighteen days to large doses of griseofulvin (total of 16 g.). J. M.